REMARKS

Claims 1, 6, 8 and 9 have been amended. Claims 3 and 11-15 have been cancelled. Applicants reserve the right to pursue the subject matter of the cancelled claims in a future application. New method of treatment claims 16-21 have been added. After entry of this amendment, claims 1, 2, 4-10 and 16-21 will be pending.

Claim 1 has been amended as follows:

- the scope of variable D has been limited by deletion of the groups -C(O)-, -O(C(O)- and a direct bond;
- the piperazinyl nitrogen is required to be substituted by R^4-D;
- "heterocyclic groups," as recited for variables R^4-R^8, have been limited to morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, isothiazolyl, indolyl, quinolyl, thienyl, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, pyridine-*N*-oxide and quinoline-*N*-oxide. Support for this amendment can be found in the specification, for example, at page 6, lines 20-25.

Applicants reserve the right to pursue any subject matter lost through these amendments in a future application. As a result of limiting the scope of variable D and requiring that the piperazinyl nitrogen is substituted, the proviso language of i) – vii) in claim 1 has been deleted as no longer necessary.

Claim 6 has been amended to reflect the limitation in scope of variable D in claim 1.

Claims 8 and 9 have been amended to clarify that they both depend from claim 1.

New method of treatment claims 16-21 find support in the specification at, for example, page 3, lines 3-11 and page 29, line 27 through page 30, line 6.

No new matter has been introduced by any of the new claims or claim amendments.

I. OBJECTION UNDER 37 C.F.R. § 1.72(b)

The Examiner objects to the lack of an abstract of the disclosure as required by 37 C.F.R. § 1.72(b).

Applicants have included an abstract of the disclosure for inclusion in the specification as a separate sheet of paper.

II. REJECTION UNDER 35 U.S.C. § 112, second paragraph

Claims 1, 2, 4-10 and 13-15 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. The specific issues raised by the Examiner are summarized and addressed below.

(a) Proviso Language

According to the Examiner, the proviso at the end of claim 1 is unclear since it recites the exclusion of certain choices for R^3 only, but actually lists moieties that include substitution at the 4-position of the piperazinyl ring, and should therefore also include R^4 and D in the limiting language of the claim. The Examiner also states that proviso i) would seem to cover iv) and vii).

Because of the amendments made to claim 1 that limit the scope of variable D and that require substitution of the piperazinyl nitrogen by R^4-D, Applicants believe that the proviso language of i) –vii) is no longer necessary and have therefore deleted it in its entirety. The deletion of the proviso language moots this ground for rejection.

(b) Scope of Method Claim 13

The Examiner objects to the scope of method claim 13 as reciting the treatment of any and all uses based on reduced PDH activity. According to the Examiner, such a scope is not readily ascertainable.

While the Applicants do not agree with the Examiner's assessment that the scope of use of claim 13 is indeterminate, Applicants have, in order to expedite prosecution of this application, deleted claims 13-15 and added new claims 16-21 that target particular disease states. As discussed above, new claims 16-21 find ample support in the specification. Applicants reserve the right to pursue any subject matter that is deleted by the cancellation of claims 13-15, and not subsequently covered by new claims 16-21, in a future application. By deleting claim 13, Applicants have mooted this ground for rejection.

(c) Claims 8 and 9

The Examiner states that claims 8 and 9 are rejected because they both recite formula (I), which is present in claim 1 but not in these claims. Therefore, the Examiner suggests that claims 8 and 9 be made either dependent on claim 1 or independent.

Applicants have amended claims 8 and 9 to make them dependent on claim 1. As such, Applicants request that this ground for rejection be withdrawn.

III. REJECTION UNDER 35 U.S.C. § 112, first paragraph

Claims 1, 2, 4-7, 9-10 and 13-15 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The specific issues raised by the Examiner are addressed below.

(a) Functional Group Variety / Lack of Direction

The Examiner objects to the scope of the functional groups claimed for each variable of formula (I) as not being adequately enabled by Applicants's specification, and cites, as an example, heterocycles, both mono- and bicyclofused, having from 4 to 12 atoms with any number of O, S and N atoms in any array and degree of unsaturation. The Examiner states that while assays measuring pyruvate dehydrogenase elevating activity are described in the specification, there is no supporting data reported. Because the specification discloses that compounds of the invention were prepared for testing, the Examiner states the presumption that only the prepared compounds recited in claim 8 were tested and found to be active. It is the Examiner's contention that the lack of test data does not allow any structure-activity trends to be evaluated and that there is no assurance of which particular substituents, other than the ones present in the compounds of claim 8, will contribute to the desired PDH elevating activity. As support for her argument, the Examiner cites the data in Table 2 of J. Med. Chem. 43(2), 236-249 (2000) to Aicher *et al.* ("*Aicher I*") as showing widely varying pyruvate dehydrogenase kinase activity for compounds of a narrower scope than the compounds encompassed by Applicants' claim 1. Therefore, according to the Examiner, it is the combination of the breadth of the scope of claim 1, the level of unpredictability in the art and the lack of direction (*i.e.* working examples) provided as to what other moieties may be effective that results in the enablement rejection being applied.

Applicants have amended claim 1 to limit the recitation of "heterocyclic group" to the following specific ring systems: morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, isothiazolyl, indolyl, quinolyl, thienyl, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, pyridine-*N*-oxide and quinoline-*N*-oxide. Support for this amendment can be found, for example, in the specification at page 6, lines 20-25. Applicants believe that the incorporation of this limitation into claim 1 directly addresses the Examiner's overall concerns regarding unpredictability in the art and lack of direction as to which moieties might be effective in elevating PDH activity. Therefore, Applicants request that this ground for rejection be withdrawn.

(b) Scope of Method Claim 13

The Examiner objects to the scope of uses within method claim 13 as not being adequately enabled based on what is currently known in the art for compounds that act as PDH inhibitors. The *Aicher*, *Mann* and *Bebernitz* references included in Applicants' IDS are cited by the Examiner as showing, at best, only a correlation for the compound uses recited in claims 14 and 15. It appears that the Examiner considers sepsis and Alzheimers disease, as additional targets of the compounds of Applicants' invention, to be either unusual, difficult to treat or speculative. The Examiner states that in such cases, evidence may be required that the tests relied on are reasonably predictive by those skilled in this art of *in vivo* efficacy.

Applicants respectfully disagree with the Examiner's assessment of the level of enablement provided by the references cited in Applicants' IDS for teaching that compounds with PDH elevating activity would be predicted to be efficacious in the treatment of disease states other than those recited in claims 14 and 15. In particular, Applicants point the Examiner to page 3, lines 10-11 of the specification where a reference is cited that specifically associates elevation of PDH activity with the treatment of Alzheimers disease. On the other hand, the Examiner has not provided any support for his statement that the treatment of Alzheimers disease or sepsis by administration of Applicants' claimed compounds is somehow unusual, difficult to treat or speculative. Applicants request that this rejection be withdrawn.

IV. REJECTION UNDER 35 U.S.C. § 102(b)

Claims 1, 2, 4-7, 9, 10 and 13-15 are rejected under 35 U.S.C. § 102(b) as being anticipated by J. Med. Chem. 42(15), 2741-2746 (1999) to Aicher *et al.* ("*Aicher II*"). According to the Examiner, *Aicher II* published on the Internet on July 14, 1999 and describes several compounds within the scope of Applicants' claims having the same activity and used for the treatment of similar disease states. As support, the Examiner cites page 2741 of *Aicher II* for a disclosure of the list of uses and page 2742 for disclosure of compounds 3m-3r.

The Examiner also rejects the first process of claim 9 because, according to the Examiner, *Aicher II* employs HO-protected acid chloride derivatives which are subsequently deprotected in step b as shown in Scheme 3 on page 2742.

Applicants believe that as amended, claim 1 can be clearly distinguished from the piperazines described in *Aicher II*. For example, *Aicher II* compounds 3m, 3o and 3r each require a -C(O)- or –O-C(O)- linkage at the piperazinyl nitrogen. In contrast, variable D of Applicants' claim 1, which directly attaches to the piperazinyl nitrogen of formula (I), has been limited such that -C(O)- and -OC(O)- are not acceptable moieties. In *Aicher II* compound 3p, the piperazinyl nitrogen is substituted with a benzyl group. By Applicants' amendment of claim 1 such that variable D cannot be a direct bond, a benzyl group is not a possible substituent for the piperazinyl nitrogen of formula (I). *Aicher II* compounds 3n and 3q have no substitution on the piperazinyl nitrogen. As amended, claim 1 is limited to N-substituted piperazinyl compounds of formula (I). For at least these reasons, the compounds of formula (I) as recited in Applicants' claim 1, as amended, are not taught or suggested by *Aicher II*. Applicants therefore request that this rejection be withdrawn. Further, because Applicants' compounds are distinguishable over the compounds described in *Aicher II*, the Examiner's rejection of process claim 9 should also be withdrawn.

V. REJECTION UNDER 35 U.S.C. § 102(a)

Claims 1, 2, 4-7, 10 and 13-15 are rejected under 35 U.S.C. § 102(a) as being anticipated by *Aicher I*. Although the Examiner states that she recognizes that Applicants are claiming benefit under 35 U.S.C. § 119 of a priority application filed September 4, 1999,

which predates the publication date of *Aicher I*, the Examiner contends that because Applicants' claims lack enablement under 35 U.S.C. § 112, *Aicher I* is a competent reference.

Applicants believe that these rejected claims find support in the priority applications, as the Examiner has observed. Therefore, once Applicants have established enablement of the claims by the present specification, the ground for this rejection will be mooted by the fact that the claimed priority filing dates antedate the January 2000 publication date of *Aicher I*.

VI. CONCLUSION

All remaining grounds for rejection have been addressed and overcome by the above amendments and remarks. It is therefore believed that all claims presently pending in this application are allowable. Accordingly, the withdrawal of all grounds for rejection and the allowance of all claims are respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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